

## Immunosuppressants Affect Human Neural Stem Cells In Vitro but Not in an In Vivo Model of Spinal Cord Injury.

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**Authors:** Christopher J Sontag, Hal X Nguyen, Noriko Kamei, Nobuko Uchida, Aileen J Anderson, Brian J Cummings

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### Public Summary:

Clinical immunosuppression protocols use calcineurin inhibitors, such as cyclosporine A (CsA) or tacrolimus (FK506), or mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus (rapamycin). These compounds alter immunophilin ligand signaling pathways, which are known to interact downstream with mediators for human neural stem cell (hNSC) differentiation and proliferation, suggesting that immunosuppressants may directly alter hNSC properties. We investigated whether immunosuppressants can exert direct effects on the differentiation, proliferation, survival, and migration of human central nervous system-derived stem cells propagated as neurospheres (hCNS-SCNs) in vitro and in an in vivo model of spinal cord injury. We identified unique, immunosuppressant-dependent effects on hCNS-SCNs differentiation and proliferation in vitro. All immunosuppressants tested increased neuronal differentiation, and CsA and rapamycin inhibited proliferation in vitro. No immunosuppressant-mediated effects on hCNS-SCNs survival or migration in vitro were detected. These data suggested that immunosuppressant administration could alter hCNS-SCNs properties in vivo. We tested this hypothesis by administering immunosuppressants to constitutively immunodeficient spinal cord injured mice and assessed survival, proliferation, differentiation, and migration of hCNS-SCNs after 14 weeks. In parallel, we administered immunosuppressants to immunocompetent spinal cord injury (SCI) mice and also evaluated hCNS-SCNs engraftment and fate. We identified no effect of immunosuppressants on the overall hCNS-SCNs fate profile in either xenotransplantation model. Despite a lower level of human cell engraftment in immunocompetent SCI mice, functional locomotor recovery was observed in animals receiving hCNS-SCNs transplantation with no evidence of allodynia. These data suggest that local cues in the microenvironment could exert a stronger influence on hCNS-SCNs than circulating levels of immunosuppressants; however, differences between human and rodent metabolism/pharmacokinetics and xenograft versus allograft paradigms could be determining factors.

### Scientific Abstract:

Clinical immunosuppression protocols use calcineurin inhibitors, such as cyclosporine A (CsA) or tacrolimus (FK506), or mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus (rapamycin). These compounds alter immunophilin ligand signaling pathways, which are known to interact downstream with mediators for human neural stem cell (hNSC) differentiation and proliferation, suggesting that immunosuppressants may directly alter hNSC properties. We investigated whether immunosuppressants can exert direct effects on the differentiation, proliferation, survival, and migration of human central nervous system-derived stem cells propagated as neurospheres (hCNS-SCNs) in vitro and in an in vivo model of spinal cord injury. We identified unique, immunosuppressant-dependent effects on hCNS-SCNs differentiation and proliferation in vitro. All immunosuppressants tested increased neuronal differentiation, and CsA and rapamycin inhibited proliferation in vitro. No immunosuppressant-mediated effects on hCNS-SCNs survival or migration in vitro were detected. These data suggested that immunosuppressant administration could alter hCNS-SCNs properties in vivo. We tested this hypothesis by administering immunosuppressants to constitutively immunodeficient spinal cord injured mice and assessed survival, proliferation, differentiation, and migration of hCNS-SCNs after 14 weeks. In parallel, we administered immunosuppressants to immunocompetent spinal cord injury (SCI) mice and also evaluated hCNS-SCNs engraftment and fate. We identified no effect of immunosuppressants on the overall hCNS-SCNs fate profile in either xenotransplantation model. Despite a lower level of human cell engraftment in immunocompetent SCI mice, functional locomotor recovery was observed in animals receiving hCNS-SCNs transplantation with no evidence of allodynia. These data suggest that local cues in the microenvironment could exert a stronger influence on hCNS-SCNs than circulating levels of immunosuppressants; however, differences between human and rodent metabolism/pharmacokinetics and xenograft versus allograft paradigms could be determining factors.

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